UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/790,540	01/30/1997	WILLIAM D. HUSE	P-IX-2405	1555

23601 7590 06/17/2003

CAMPBELL & FLORES LLP
4370 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/17/2003

92

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/790540	HUSE	
	Examiner	Art Unit	
	GAMBEL	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 2/28/03

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 1-39

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 19-25

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected. 1-18, 26-39

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission, filed on 2/28/03 (Paper No. 40), has been entered.

Applicant's amendment, filed 2/28/03 (Paper No. 41), has been entered.
Claim 33-39 have been added.

Claims 1-18 and 26-39 are under consideration in the instant application.

Claims 19-25 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a nonelected invention.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
The rejections of record can be found in previous Office Actions (Paper Nos. 5/8/13/16/20/25/29/35).

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

A more thorough review of applicant's arguments and the examiner's rebuttal of record can be found in Paper Nos. 29/35 or reiterated herein for applicant's convenience.

3. Claims 1, 2, 9,10, 12-18 and 32 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "having 88% / 79% or greater identity

Applicant's arguments in conjunction with certain legal decisions, filed 2/28/03 (Paper No. 41), were fully considered and not found convincing for the reasons of record set forth in Paper Nos. 20/25/29/35.

Applicant's arguments and the examiner's rebuttal are essentially the same of record

Applicant argues that the test of sufficient written description is whether the disclosure of the application as originally filed reasonably conveys to a person skilled in the art that the invention had possession of the claimed subject matter at the time of the earlier filing date.

Applicant argues the that the specification need not provide literal support for the claim language but, rather, convey to one skilled in the art that applicant was in possession of the claimed invention at the time the application was filed.

Applicant relies upon various teachings in the specification as-filed to support modifications and substantially the same sequences as set forth in SEQ ID NOS 2/4.

Again, it is acknowledged that the claims have been amended from "having greater than 88% / 79% identity" to "having 88% / 79% or greater identity"; the issues have been the same.

Again, applicant's amendment, filed 9/1/01 (Paper No. 32), directs support to pages 45 - 48 and to various other passages in the specification as-filed for these above-mentioned "limitations". Applicant has relied upon the teaching of the specification (e.g. pages 20-21) disclosing methods that can be used to change any or all of the non-identical amino acids either alone or in combination. Applicant has asserted that the ordinary artisan would have understood that the substitution of any, but less than all of the amino acids would have resulted in the claimed limitations.

As pointed out previously, while the specification as filed provides for 'CL had "88/79%" identity to frameworks 1, 2 and 3 of LM609 heavy chain/light chain; there is insufficient written description for " and greater" as well as "at least one LM609 CDR-grafted heavy/light chain polypeptide comprising a variable region amino acid sequence greater than 88%/79% identity with that shown in Figure 1A/1B" or "functional fragments" thereof, or "nucleic acids" encoding the same; as currently recited..

The specification as filed does not provide sufficient written description for the above-mentioned claimed "limitations", as they are currently recited. Applicant's reliance on generic disclosure and possibly a single species does not provide sufficient direction and guidance to the "currently claimed limitations". It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it. Also, see MPEP 2163.05 Changes to the Scope of Claims.

It appears that applicant has acknowledged that these particular "terms and phrases" do not have written description in the specification as filed; therefore the claims represent a departure from the specification and claims as originally filed. Applicant's reliance on generic disclosure and possibly a single or limited species has not provided sufficient direction and guidance to the "features" currently claimed. It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action

Again, applicant is invited to provide sufficient written support for the "limitations" indicated above.

Applicant's arguments have not been found persuasive

4. Claims 1-18, 26-39 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter for the reasons of record.

Applicant's arguments, filed 2/28/03 (Paper No. 41), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments in conjunction with certain legal decisions have been fully considered but are not found convincing essentially for the reasons of record.

As pointed out previously; applicant's arguments, in conjunction with the Huse declaration have been as well as U.S. Patent No. 5,753,230 (1449) and Biotechnology Newswatch Biotechnology Newswatch (1/16/95) presented an ambiguity with regard to the inventorship of the claimed invention.

It is noted that upon further review, Dr. Glaser is a co-inventor of the claimed subject matter and a Declaration by the actual inventors and other requirements under 35 USC 1.48(a) will be forthcoming in a supplemental response.

Applicant maintains that the inventorship has been reviewed and determined to be correct and that both Huse and Glaser have been determined to be inventors of the claimed compositions, wherein the claimed compositions have specifically recited SEQ ID NOS.

As pointed out previously; it was noted that the Huse Declaration, filed 12/14/98 (Paper No. 12) indicates that he conceived the idea of humanizing $\alpha_v\beta_3$ inhibitory antibodies.

It is noted that the Huse/Glaser Declaration under 37 C.F.R. § 1.132, filed 6/12/00 (Paper No. 23), states that both Huse and Glaser are joint inventors of the instant claims

Huse avers in the Declaration that the sequences of the claimed antibodies and encoding nucleic acids were not known prior to cloning and sequencing of the LM609 heavy and light chain variable region and generation of LM609 grafted antibodies at Ixsys. The Declaration states that the LM609 hybridoma was brought to Ixsys, Inc., where the LM609 heavy and light chain variable region cDNA was cloned.

Applicant argues that conception of the claimed compositions having specifically recited SEQ ID NOS requires the determination of the nucleotide sequence of the LM609 heavy and light chain variable regions and the use of determined sequences to generate the claimed grafted antibodies having specifically recited SEQ ID NOS.

Applicant asserts that the Declaration indicates that neither Cheresh nor Brooks suggested or contributed to the cloning, sequencing, humanizing or making the claimed antibodies and nucleic acids.

Applicant has maintained that Cheresh and Brooks could be considered, at most, technical collaborator but not an inventor of the claimed antibodies and nucleic acids referenced as specifically recited SEQ ID NOS.

The test for conception is whether inventor had an idea that was definite and permanent enough that one skilled in the art could understand the invention; an idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand; and it must also be sufficiently precise that a skilled artisan could carry out the invention without undue experimentation. For example, see Burroughs Wellcome Co. v. Barr Laboratories Inc. 32 USPQ2d 1915 (CAFC 1994).

However, applicant has not provided sufficient objective evidence or information to address either the contribution of Glaser to the claimed invention, given the first Huse Declaration, filed 12/14/98 (Paper No. 12), which indicated that he alone conceived the idea of humanizing $\alpha_v\beta_3$ inhibitory antibodies or the contribution of Cheresh as a scientific collaborator, but not as an inventor.

Applicant maintain that based on the evidence of record, neither Drs. Cheresh nor Brooks can be considered inventors of the claimed compositions having specifically recited SEQ ID NOS in view of the position of the Federal Circuit with respect to inventorship. The inventors is the person or persons who conceived the patent inventions and for certain inventions, including nucleic acids, conception occurs simultaneously with reduction to practice.

Applicant maintains that conception of the claimed compositions having specifically recited SEQ ID NOS requires the determination of the nucleotide sequence of the LM609 heavy and light chain variable regions and the use of the determined sequences to generate the claimed grafted antibodies having specifically recited SEQ ID NOS. Applicant maintains the sequence of the LM609 antibody was determined at Ixsys, Inc., where LM609 CDR-grafted antibodies were generated and developed.

Applicant maintains that nay description of a humanized LM609 antibody in U.S. Patent No. 5,753,230 is a statement of a problem to be solved because there is no completion of the mental part of the invention. Applicant argues that significantly U.S. Patent No. 5,753,230 provides no description of any nucleotide or amino acid sequence of LM609 or humanized LM609 antibody and lacks a description of a definite and permanent idea of the complete and operative invention.

Applicant maintains that the Biotechnology Newswatch article do not raise issues of ambiguity with respect to inventorship because the article do not provide any description of any nucleotide or amino acid sequence of LM609 or humanized LM609 antibody. Further, the Biotechnology Newswatch article clearly state that the rights to modify the antibody LM609 have been licensed to Ixsys, Inc and that Ixsys, Inc. has developed a humanized venison of LM609.

Applicant argues that the method of obtaining a nucleotide sequence of LM609 or the nucleotide or amino acid sequence of LM609 CDR-grafted antibodies is irrelevant

Again, as pointed out previously, applicant has not provided the facts concerning the nature and role of Cheresh as a collaborator, with respect to humanizing the LM609 antibody. It is noted that Biotechnology Newswatch acknowledges that Cheresh was the principal investigator. It is clear that Cheresh developed the LM609 antibody and that it was possible to determine without undue experimentation antibodies and humanized antibodies having the same properties (see U.S. Patent No. 5,753,230, particularly columns 15-19). Further, U.S. Patent No. 5,753,230 claims the use of LM609 antibody as well as humanized versions thereof. Similarly the instant specification acknowledges that Cheresh developed the LM609 antibody (see page 9, for example) and that generating humanized/CDR-grafted antibodies were known in the art at the time the invention was made (see page 17, for example). Again, it is clear that given U.S. Patent No. 5,753,230 that humanizing $\alpha_v\beta_3$ inhibitory antibodies, including the LM609 antibody was known in the prior art by others. Again, it is noted that Brooks was an inventor on U.S. Patent No. 5,753,230.

Further, the proposition that the Biotechnology Newswatch article and U.S. Patent No. 5,753,230 failed to provide the structure of the claimed LM609 CDR-grafted antibody precludes the teachings thereof from serving as evidence to establish a prima facie case of obviousness is contrary to a body of law which holds that a product may be described by the process of making it. As pointed in Ex parte Goldgaber, 41 USPQ2d 1173, 1176 BPAI 1996), there is nothing intrinsically wrong in the application of methodology in the rejection product claims under 35 USC 103 depending on the particular facts of the case, the manner and context in which methodology applies and their overall logic of the rejection. Nor does Bell or Deuel issue a blanket prohibition against the application of methodology in rejecting product claims defining DNA of cDNA. It is perfectly acceptable to consider the method by which a compound is made in evaluating the obviousness of the compound. In determining obviousness, it is appropriate to consider such matters as the manner of preparation of the composition vis-a-vis the prior art, the structural similarities as well as differences between the claimed composition and that of the prior art and the presence or absence of properties which would unobvious in view of the prior art. See In re Pilkington, 411 F.2d 1345, 162 USPQ 145 (CCPA 1969); In re Best, 562, F.2d 1252, 195 USPQ 430 (CCPA 1977). The Federal Circuit has recognized that a gene, being a chemical compound , could be defined "by its methods of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguished it (from other materials)." See Amgen, 927 F.2d 1200 at 1206, 18 USPQ2d at 1021 (Fed. Cir., 1991); Fiers V. Sugano, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993). As noted in In re Cofer, 354, F.2d 664, 148 USPQ 268 (CCPA 1966), the particular structure or form of a chemical compound is an important consideration in determining obviousness under 35 USC 103; but it is not the only consideration. A compound may well be defined or described by characteristics other than its chemical structure. Though those skilled in the art may be unaware of the exact chemical structure of an antibody they are aware that is it composed of established relatively unchanging (array of nucleotides which code for the particular protein) . Importantly, they are also aware that the probe will hybridize with the targeted antibody or immunoglobulin of interest. Those skilled in the art are also aware of established procedures for isolating the gene using the hybridization phenomenon. Such procedures are taught in the references of record and employed by appellant in the instant disclosure.

Therefore, the ordinary artisan would have made the instant CDR-grafted LM609 antibody and, in turn, would have made the cDNA of said CDR-grafted LM609 antibody with a reasonable expectation of success, given the availability of the LM609 antibody/hybridoma taught and acknowledged by applicant in the prior art as well as the claimed humanized LM609 of U.S. Patent No. 5,753,230.

Applicant's arguments are not found persuasive.

5. Claim 26 and newly added claims 33-39 are rejected under 35 U.S.C. § 102(e) as being anticipated by Brooks et al. (U.S. Patent No. 5,753,230) essentially for the reasons of record set forth in Paper Nos. 16/20/25/29/35.

Applicant's arguments in conjunction with the Huse declaration under 37 C.F.R. § 1.132 of record, have been fully considered but are not found convincing essentially for the reasons of record.

Again, applicant argues that to anticipate a claim, the reference must teach every element of the claim and that absent a teaching of the structural features other antibody specifically recited in the claims as SEQ ID NOS: 1 and 3 (and presumably SEQ ID NO:S 2 and 4); the rejection of record should be withdrawn.

Given that claim 26 and newly added claims 233-39 recite "of a modification thereof or a functional fragments of said LM609 CDR-grafted antibody" and the prior art teaching of humanized LM609 antibodies; applicant's arguments concerning the particular structural characteristics of the claimed limitations have not been found persuasive. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed "limitations" read on "modifications thereof or a functional fragments of said LM609 CDR-grafted antibody"

Applicant's arguments relying upon the particular SEQ ID NOS: recited in the instant claims do not obviate the prior art teaching, as it reads on "a modification thereof or a functional fragments of said LM609 CDR-grafted antibody" of the same LM609 antibody of the claimed invention.

Applicant's arguments are not found persuasive.

6. Claims 1-18 and 26-321 and newly added claim 33-39 rejected under 35 U.S.C. § 103 as being unpatentable over Brooks et al. (U.S. Patent No. 5,753,230; 1449) in view of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof, as disclosed on pages 3-37 or Examples I and II of the instant specification or as cited by references on the 1449 for the reasons of record set forth in Paper Nos. 16/20/25/29/35..

The teachings of Brooks et al. in view of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof, as disclosed on pages 10-39 or Examples I and II of the instant specification or as cited by references on the 1449 are of record. Briefly, teach the LM609 antibody as well as humanized forms of this antibody and claim methods of using the LM609 antibody as well as humanized forms of this antibody (see entire document, particularly columns 15-19 and the claims). With respect to specific amino acid changes including those which are "modifications" would be obvious given the teachings of humanized LM609 antibodies and art known methods to generate such humanized antibodies which retain the desired functional characteristics of the native antibody and to alter said antibody for therapeutic uses, including human therapy, as taught and known in the prior art.

Applicant's arguments in conjunction with the Huse/Glaser declarations under 37 C.F.R. § 1.132 of record have been fully considered but are not found convincing essentially for the reasons of record.

Again, applicant's arguments and the examiner's rebuttal are essentially the same as of record, which are reiterated herein for applicant's convenience.

Again applicant arguments have essentially focused on whether the prior art taught the particular structural features of the LM609 antibody, particularly the nucleic acid or amino acid sequences of the LM609 antibody. Applicant argues that the prior art teaching does not teach or suggest the claimed compositions having specifically recited SEQ ID NOS.

Applicant has argued that the claims recite structural characteristics which are not taught or suggested in any of the cited references. Applicant has argued that Brooks et al. do not teach or suggest the claimed human acceptor framework sequences LM609 CDR's, encompassed by SEQ ID NOS: 2, 3, 32, including the amino acid at position 49. Applicant asserts that the change of amino acid to three other amino acids unexpectedly results in functional antibody having integrin $\alpha v\beta 3$ binding activity.

Applicant has argued in conjunction with Deuel that the prior art, including Brooks et al. does not teach nor suggest the nucleic acids having the structural characteristics of the specifically recited SEQ ID NOS.

Applicant has argued that the prior art describes the mouse antibody and not applicant's claimed non-mouse antibodies having human acceptor framework sequences with LM609 CDR's

Applicant has argued that Padlan teaches away from the claimed invention.

Applicant has argued in conjunction with the Huse Declaration that there were difficulties in cloning authentic DNA sequences.

The following is provided for applicant's convenience.

As pointed out previously; the amino acid and nucleic acid sequences associated with the LM609 antibody including those of humanized LM609 antibodies would have been available to the ordinary artisan, given the availability of the LM609 antibody and hybridoma together with general immunoglobulin gene cloning and expression strategies. It would have been have been a matter of routine experimentation well within the ordinary skill level of art to generate chimeric or humanized LM609 antibodies, DNA encoding said antibodies. Given the highly conserved nature of immunoglobulin gene organization and structure and the availability of probes and PCR primers for immunoglobulin gene cloning, one of ordinary skill in the art could have isolated the functionally rearranged heavy and light chain variable regions from the LM609 hybridoma cell line and determined their sequences with a complete expectation of success. For example, the ordinary artisan does not need to determine the amino acid sequences of a rearranged V (variable) region before cloning. The claims do not differ unexpectedly or unobviously from what one of ordinary skill in the art would have expected to obtain given the known LM609 hybridoma thereof, the known heavy and light chain and the art known techniques regarding the production of chimeric antibodies, as acknowledged by the number of available art known procedures disclosed in the instant specification and cited on the Information Disclosure Statement. The claimed DNA sequences must encode a recombinant antibody comprising heavy and/or light chain variable regions of the LM609 antibody.

Immunoglobulin gene structure and organization were well understood in the art a the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs encoding immunoglobulin variable regions. In addition, it was known at the time the invention was made that the benefits of producing recombinant antibodies to reduce the immunogenicity of therapeutic and diagnostic antibodies in human patients. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

As pointed out in the previous Office Actions, it was noted that the instant disclosure relied upon standard humanization procedures to derive the claimed antibody and nucleic acid compositions. Also, it was noted that Biotechnology Newswatch (1/16/95 and 2/6/95) references above support the routine nature of providing an antibody/hybridoma of interest to a commercial interest to develop humanized antibodies and the nucleic acids encoding said antibodies by routineers in the art at the time the invention was made.

In contrast to applicant's assertions and for the reasons of record and reiterated above; the claimed antibodies and nucleic acids do not differ unexpectedly or unobviously from what one of ordinary skill in the art would have expected given the availability of the LM609 antibody and hybridoma in the prior art as well as the art known techniques regarding the production of chimeric and humanized antibodies at the time the invention was made, as acknowledged by the number of available art known procedures disclosed in the instant specification and cited on the Information Disclosure Statement.

For example, page 15, paragraph 1 of the specification discloses that functional replacement of the CDRs was performed by recombinant methods known to those skilled in the art, commonly referred to as CDR grafting. Also, page 20, paragraph 1 of the specification discloses that identification of amino acids to be changed can be accomplished by those skilled in the art using current information available regarding the structure and function of antibodies as well available and current information encompassing methods for CDR grafting procedures. In addition, page 20, paragraph 2 of the specification discloses using the above described methods known within the art, any or all of the non-identical amino acids can be changed either alone or in combination with amino acids at different positions to incorporate the desired number of amino acid substitutions at each of the desired positions. Page 21, paragraph 1 discloses that the functional replacement of amino acids is beneficial when producing grafted antibodies having human framework sequences since it allows for the rapid identification of equivalent amino acid residues without the need for structural information or the laborious procedures necessary to assess and identify which amino acid residues should be considered for substitution in order to successfully transfer binding function from the donor. Also see (Singer et al., J. Immunol. 150: 2844-2857, 1993 and Padlan, Mol. Immunol 28: 489-498, 1991 of the Information Disclosure Statement; which provide for art known procedures and expectation of success in humanizing known antibodies of interest, including deriving the appropriate changes to derive the desired reduction in reduced immunogenicity and in desired specificity. The claimed grafted antibodies and associated nucleic acids were predictable by the known and practiced means (e.g. computer modeling) at the time the invention was made. It is noted that Padlan discloses the same procedures using the same frameworks in procedures for reducing the immunogenicity of antibody variable domains while preserving their ligand-binding properties as relied upon in applicant's claimed invention (see entire document).

Therefore, it appears that applicant has relied upon the same starting material as the prior art (LM609 antibody and hybridoma) and that applicant has relied upon the same recombinant means to derive the same antibodies and nucleic acids derived from humanizing the LM609 antibody taught and claimed by the prior art. It is clear that Brooks et al. teach antibodies that have the same or similar immunoreactive characteristics and compete for binding to the same preselected target molecule as the LM609 antibody (see columns 15-18, particularly column 17). In contrast to applicant's assertions; humanizing the LM609 antibody or modifying humanized LM609 antibody and its associated nucleic acids in achieving the claimed limitations was known and obvious, given the same starting materials, including the LM609 antibody/hybridoma and acceptor molecules and given the same recombinant means to achieve the same humanized antibodies as clearly taught and known in the prior art. As pointed out above, the modifications other than simple CDR-grafted LM609 antibody appear to be predictable or to be predicated on the same standard and known computer modeling in the prior art in humanizing antibodies of interest.

Also as pointed out above, for examination purposes under art; the recitation of 'a modification thereof that does not change the encoded amino acid sequence" reads on modifications which do not change the encoded amino acid sequence due to the degeneracy of the genetic codes as well as those which result in only a conservative substitution of the encoded amino acid sequence. Such modifications would have resulted in humanized LM609-specific antibodies encompassed by the claimed invention.

Also, the claims recited functional fragments thereof and again; such limitations would have been obvious in view of the prior art teaching of generating humanized LM609-specific antibodies.

Applicant's arguments are not found persuasive.

7. Claims 1-18 and 26-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over pending claims of
copending application USSN 08/791,391;
copending application USSN 09/016,061 and
copending application USSN 09/900,590 essentially for the reasons of record.
This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant and copending claims are drawn to CDR-grafted and humanized LM609 antibodies and nucleic acids that encode said antibodies that appear to anticipate one another.

It is acknowledged that certain LM609-specific modifications recited in copending applications may be considered unobvious species of humanzied LM609 antibodies and nucleic acids that encode said antibodies.

Applicant is invited to distinguish the instant claims from the copending claims.

USSN 08/791,391 and 09/016,061 are not available to the examiner at this time.

Again, applicant's amendment request that this provisional ground of rejection be deferred until there is an indication of allowable subject matter

Applicant has provided for the common ownership of the instant application with USSN 08/791,391.

Given applicant's intent to amend the inventorship of the instant application, applicant is invited to provide evidence of common ownership of the other copending applications, if appropriate.

Alternatively, commonly assigned copending USSNs 08/791,391; 09/016,061 and 09 09/900,590/, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
June 13, 2003